Mirabegron and Solifenacin in the Treatment of Overactive Bladder

Krista Trinidad, PA-S

Faculty Advisor: Elizabeth Masten, PA-C

Department of Medical Science

Abstract

Overactive bladder is a condition where the bladder muscles contract before the bladder is full, causing the urge to urinate. The standard first line medication for overactive bladder is solifenacin, and mirabegron serves as an alternative option. Solifenacin is an anticholinergic medication that is associated with a wide range of undesirable side effects. Therefore, this review analyzes the use of a combination of solifenacin and mirabegron, compared to monotherapy with solifenacin, for symptom management in patients suffering from moderate to severe overactive bladder.

Introduction

Overactive Bladder

Overview:
- Condition involves involuntary leakage of urine
- Consists of stress urinary incontinence, overflow incontinence and urge incontinence
- Affects 17% of adults in the United States and Europe

Symptoms:
- Urinary urgency, urinary frequency, nocturia
- Can significantly reduce quality of life, leading to higher levels of anxiety and depression, reduced general health status and poorer sleep quality

Treatment:
- Conservative treatment includes weight loss, fluid reduction, bladder training, pelvic floor muscle exercises or electrical stimulation of the posterior tibial nerve.
- Pharmacologic treatment with anticholinergics, beta- adrenergic agonists, OnabotulinumtoxinA or intravaginal estrogen
- First line: Solifenacin, an antimuscarinic drug, and mirabegron, a beta- adrenergic agonist

Methods

Performed in November 2019 using:
- PubMed
- Academic Search Ultimate
- Google Scholar

Search terms: "urinary incontinence" AND "mirabegron" AND "solifenacin"

Inclusion Criteria:
1. Publish date within last 5 years
2. Randomized control trial or clinical trial

Exclusion Criteria:
1. Systematic review or meta-analysis
2. Studies involving trials with animals and not humans
3. Studies involving humans outside of adult age range

Results

1. **Abrams P, Kelleher C, Staskin D, et al. Combination treatment with mirabegron and solifenacin in patients with overactive bladder: efficacy and safety results from a randomised, double-blind, dose-ranging, phase 2 study (Symphony). European urology.**
   § RCT of 1306 participants designed to test the efficacy of mirabegron and solifenacin in combination compared to the effectiveness of monotherapy with solifenacin in the treatment of overactive bladder.
2. **Batista JE, Kölbl H, Rechberger T, et al. The efficacy and safety of mirabegron compared with solifenacin in overactive bladder patients dissatisfied with previous antimuscarinic treatment due to lack of efficacy: results of a noninferiority, randomized, phase IIIb trial - Jose E. Batista, Heinz Kölbl, Sender Herschorn, Tomasz Rechberger, Javier Cambronero, Michael Halaska, Alex Coppell, Mathilde Kaper, Moses Huang, Emad Siddiqui, , 2015. SAGE Journals.**
   § RCT of 1887 participants designed to test the efficacy of mirabegron and solifenacin in combination compared to the effectiveness of monotherapy with solifenacin in the treatment of overactive bladder.
3. **Drake MJ, Chapple C, Esen AA, et al. Efficacy and Safety of Mirabegron Add-on Therapy to Solifenacin in Incontinent Overactive Bladder Patients with an Inadequate Response to Initial 4-Week Solifenacin Monotherapy: A Randomised Double-blind Multicentre Phase 3B Study (BESIDE). European urology.**
   § RCT of 2174 participants designed to test the efficacy of mirabegron and solifenacin in combination compared to the effectiveness of monotherapy with solifenacin in the treatment of overactive bladder.
4. **Gratzke C, van Maanen R, Chapple C, et al. Long-term Safety and Efficacy of Mirabegron and Solifenacin in Combination Compared with Monotherapy in Patients with Overactive Bladder: A Randomised, Multicentre Phase 3 Study (SYNERGY II). European urology.**
   § RCT of 1829 participants designed to test the efficacy of mirabegron and solifenacin in combination compared to the effectiveness of monotherapy with solifenacin in the treatment of overactive bladder.
5. **Herschorn S, Chapple CR, Abrams P, et al. Efficacy and safety of combinations of mirabegron and solifenacin compared with monotherapy and placebo in patients with overactive bladder (SYNERGY study). BJU international.**
   § RCT of 3527 participants designed to test the efficacy of mirabegron and solifenacin in combination compared to the effectiveness of monotherapy with solifenacin in the treatment of overactive bladder.
6. **Kosilov K, Loparev S, Ivanovskaya M, Kosilova L. A randomized, controlled trial of effectiveness and safety of management of OAB symptoms in elderly men and women with standard-dosed combination of solifenacin and mirabegron. Archives of gerontology and geriatrics.**
   § RCT of 239 participants designed to test the efficacy of mirabegron and solifenacin in combination compared to the effectiveness of monotherapy with solifenacin in the treatment of overactive bladder.
7. **MacDiarmid S, Al-Shukri S, Pavlov SA-S, et al. Mirabegron as Add-On Treatment to Solifenacin in Patients with Incontinent Overactive Bladder and an Inadequate Response to Solifenacin Monotherapy. The Journal of Urology.**
   § RCT of 2174 participants designed to test the efficacy of mirabegron and solifenacin in combination compared to the effectiveness of monotherapy with solifenacin in the treatment of overactive bladder.

Table 1: Comparison of study designs for Mirabegron and Solifenacin vs. Monotherapy

Study	Design	Total N	Population Demographics	Age range (years)	Length of Dx at Baseline	Duration of Intervention	Control
1	RCT	1306	867 F 439 M	18 or older	≥3 months	12 weeks	solifenacin, mirabegron or placebo
2	RCT	1887	1434 F 453 M	18 or older	≥3 months	12 weeks	solifenacin 5 mg
3	RCT	2174	1757 F 353 M	18 or older	≥3 months	16 weeks	solifenacin 5 mg, solifenacin 10 mg
4	RCT	1829	1463 F 366 M	19-86 years old	≥3 months	112 months	mirabegron, solifenacin, or placebo
5	RCT	3527	2716 F 811 M	18 or older	NA	18 weeks	mirabegron, solifenacin, or placebo
6	RCT	239	NA	Average age: 71.2	≥3 months	6 weeks	solifenacin, mirabegron or placebo
7	RCT	2174	NA	18 or older	≥3 months	12 weeks	solifenacin 5 mg or solifenacin 10 mg

Discussion

6/7 studies found the greatest reduction of symptoms with solifenacin and mirabegron when compared to solifenacin only, mirabegron only, or placebo.

Strengths:
- All studies based on randomized control trial with a double-blind study design → prevents research outcomes from being affected by placebo effect or observer bias
- 6/7 studies required participants to have symptoms of overactive bladder for at least 3 months
- Recruitment methods

Limitations:
- Small sample sizes
- Short study durations with no long term follow up

Future Research:
- Studies showing efficacy and tolerability for a longer duration and larger population is needed to improve the validity of the results

Conclusion

Since only one study conducted to this date has taken place over 12 months, more follow up research should be conducted to evaluate the long-term efficacy and tolerability of the combination of mirabegron and solifenacin in the treatment of overactive bladder. In addition, future studies should aim to include a greater number of male participants, since majority of the studies discussed above consisted of mainly female participants. The prevalence of the condition is similar in both males and females, and therefore studies should look at the effectiveness of treatment regimen equally across both sexes. Trials with a larger sample size, with different racial groups, cultural groups, and co-morbidities should also be conducted. Although some of these seven studies had areas with weakness, the results from the studies as a whole may support the use of solifenacin and mirabegron together to treat overactive bladder that does not respond to monotherapy. Future research is warranted.

References:

1. Kelleher C, Hakimi Z, Zur R, et al. Efficacy and Tolerability of Mirabegron Compared with ... European Urology . https://www.europeanurology.com/article/S0302-2838(18)30201-X/fulltext. Accessed March 3, 2020.

2. Xu Y, Liu R, Liu C, Cui Y, Gao Z. Meta-Analysis of the Efficacy and Safety of Mirabegron Add-On Therapy to Solifenacin for Overactive Bladder. International Neurourology Journal. https://www.einj.org/journal/view.php?doi=10.5213/inj.1734934.467. Published September 12, 2017. Accessed March 3, 2020.

3. Hsu FC, Weeks CE, Selph SS, Blazina I, Holmes RS, McDonagh MS. Updating the evidence on drugs to treat overactive bladder: a systematic review. International urogynecology journal. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6795617/. Published October 2019. Accessed March 3, 2020.

4. Chapple CR, Mironska E, Wagg A, et al. Multicriteria Decision Analysis Applied to the Clinical Use of Pharmacotherapy for Overactive Bladder Symptom Complex. European Urology . https://www.eu-focus.europeanurology.com/article/S2405-4569(19)30296-2/fulltext. Published 2019. Accessed March 3, 2020.

5. Deeks ED. Mirabegron: A Review in Overactive Bladder Syndrome. Drugs. https://www.ncbi.nlm.nih.gov/pubmed/29869204. Published June 2018. Accessed March 3, 2020.

6. Abrams P, Kelleher C, Staskin D, et al. Combination treatment with mirabegron and solifenacin in patients with overactive bladder: efficacy and safety results from a randomised, double-blind, dose-ranging, phase 2 study (Symphony). European urology. https://www.ncbi.nlm.nih.gov/pubmed/24612659. Published March 2015. Accessed November 13, 2019.

7. Batista JE, Kölbl H, Rechberger T, et al. The efficacy and safety of mirabegron compared with solifenacin in overactive bladder patients dissatisfied with previous antimuscarinic treatment due to lack of efficacy: results of a noninferiority, randomized, phase IIIb trial - Jose E. Batista, Heinz Kölbl, Sender Herschorn, Tomasz Rechberger, Javier Cambronero, Michael Halaska, Alex Coppell, Mathilde Kaper, Moses Huang, Emad Siddiqui, , 2015. SAGE Journals. https://journals.sagepub.com/doi/full/10.1177/1756287215589250. Accessed November 13, 2019.

8. Drake MJ, Chapple C, Esen AA, et al. Efficacy and Safety of Mirabegron Add-on Therapy to Solifenacin in Incontinent Overactive Bladder Patients with an Inadequate Response to Initial 4-Week Solifenacin Monotherapy: A Randomised Double-blind Multicentre Phase 3B Study (BESIDE). European urology. https://www.ncbi.nlm.nih.gov/pubmed/26965560. Published July 2016. Accessed November 13, 2019.

9. Gratzke C, van Maanen R, Chapple C, et al. Long-term Safety and Efficacy of Mirabegron and Solifenacin in Combination Compared with Monotherapy in Patients with Overactive Bladder: A Randomised, Multicentre Phase 3 Study (SYNERGY II). European urology. https://www.ncbi.nlm.nih.gov/pubmed/29866467. Published October 2018. Accessed November 13, 2019.

10. Herschorn S, Chapple CR, Abrams P, et al. Efficacy and safety of combinations of mirabegron and solifenacin compared with monotherapy and placebo in patients with overactive bladder (SYNERGY study). BJU international. https://www.ncbi.nlm.nih.gov/pubmed/28418102. Published October 2017. Accessed November 13, 2019.

11. Kosilov K, Loparev S, Ivanovskaya M, Kosilova L. A randomized, controlled trial of effectiveness and safety of management of OAB symptoms in elderly men and women with standard-dosed combination of solifenacin and mirabegron. Archives of gerontology and geriatrics. https://www.ncbi.nlm.nih.gov/pubmed/26169181. Published 2015. Accessed November 13, 2019.

12. MacDiarmid S, Al-Shukri S, Pavlov SA-S, et al. Mirabegron as Add-On Treatment to Solifenacin in Patients with Incontinent Overactive Bladder and an Inadequate Response to Solifenacin Monotherapy. The Journal of Urology. https://www.auajournals.org/doi/abs/10.1016/j.juro.2016.03.174. Accessed November 13, 2019.